In the Claims

1. (twice amended) A method to decrease fibrous tissue size comprising administering to an individual in need of treatment thereof an effective amount of a [dematan] dermatan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

Remarks

Declaration

A new Declaration is enclosed.

Amendment

Claim 1 has been amended to correct the spelling of dermatan.

Rejections under 35 U.S.C. 103

Claims 1-11 were rejected as obvious over U.S. Patent No. 6,153,187 to Yacoby-Zeevi in combination with U.S. Patent No. 5,985,582 to Triscott. These rejections are respectfully traversed if applied to the amended claims.

U.S. patent No. 6,153,187 to Yacoby-Zeevi

Yacoby-Zeevi specifically claims the use of heparinase and heparanase for use in reducing pulmonary disease principally by reducing the viscosity of sputum. In particular this patent addresses the use of aerosolized enzymes to treat the accumulation of very thick sputum found in cystic fibrosis. The only data presented

are for heparanase, and that data is confined to showing a reduction in sputum viscosity.

Yacoby-Zeevi does not not address the issue of fibroblast proliferation nor collagen production, as claimed.

The examiner has referred to col. 6, lines 52-65, in support of his position. However, these lines specifically refer to ***decreasing the viscosity of secretions***, not reducing fibrotic tissue. As Yacoby-Zeevi accurately recognizes, the secretions in the disorders he proposes to treat consist of at least 3% glycosaminoglycans (col. 6, lines 61-62), therefore one would expect that glycosaminoglycan degrading enzymes would decrease their viscosity. There is nothing about decreasing obstructions in the airways *other than by virtue of altering the properties of the secretions*. Yacoby-Zeevi does not teach doing anything to tissue. The examiner has failed to point to any support for his position that decreasing viscosity of secretions in airways, will alter fibrotic tissue size as claimed.

U.S. patent No. 5,985,582 to Triscott

Triscott describes an assay of antithrombin in plasma. No therapeutic uses for treating patients for any disease are suggested nor mentioned. This is an *in vitro* diagnostic assay. Chondroitinases are used, but only in the context of this plasma assay.

The combination of Yacoby-Zeevi with Triscott

Yacoby-Zeevi teaches using a glycosaminoglycan degrading enzyme to degrade the glycosaminoglycans in secretions blocking the airways of patients

having diseases such as cystic fibrosis (CF). See, col. 7, lines 45-49: "the method comprising the step of administering at least one glycosaminoglycans degrading enzyme to the patient in an amount therapeutically effective to reduce at least one of the following: the visco-elasticity of the material, pathogens infectivity and inflammation." See also col. 10, lines 10-13, "a method of managing a patient having an accumulation of mucoid, mucopurulent or purulent material containing glycosaminoglcyans, typically associated with airway associated disease, such as a respiratory disease or sinusitis."

Triscott teaches selecting chondroitinase B in an *in vitro* assay.

One skilled in the art would be led *at most* to using chondroitinase B to reduce the secretions blocking the airways of patients with airway associated disease, based on the combination of Yacoby-Zeevi and Triscott. This would not result in what applicants claim:

"A method to decrease fibrous tissue size comprising

administering to an individual in need of treatment thereof

an effective amount of a dermatan sulfate or chondroitin sulfate degrading enzyme to

decrease fibrous cell proliferative response to growth factors,

reduce secretion of collagen by fibroblasts, and thereby

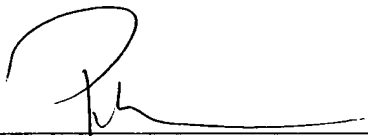
decrease the size of fibrous tissue.

Accordingly, one skilled in the art would not be led to treat patients with the

claimed enzymes to inhibit proliferation of fibroblasts. Moreover, one would not have any idea of what an effective amount is, nor how to formulate or administer an effective amount, certainly not with any reasonable expectation of success. See, in contrast, the application at pages 15-21, which not only demonstrates the mechanisms and effective dosages, but also treatment of actual disease in an animal model. Accordingly, claims 1-11 are not obvious over the cited art, alone or in combination.

Allowance of claims 1-11 is therefore earnestly solicited.

Respectfully submitted,



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Patrea L. Pabst

APPENDIX: Claims marked as Amended

1. (twice amended) A method to decrease fibrous tissue size comprising administering to an individual in need of treatment thereof an effective amount of a [dematan] dermatan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial dermatan or chondroitin sulfate degrading enzyme and is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, chondroitin sulfate degrading enzymes from *Bacteroides* species, chondroitin sulfate degrading enzymes from *Proteus vulgaris*, chondroitin sulfate degrading enzymes from *Micrococcus*, chondroitin sulfate degrading enzymes from *Vibrio* species, chondroitin sulfate degrading enzymes from *Arthrobacter aurescens*, arylsulfatase B, N-acetylgalactosamine-6-sulfatase and iduronate sulfatase from mammalian cells, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.

3. The method of claim 1 wherein the enzyme is a mammalian enzyme.

4. The method of claim 1 wherein the enzyme is a bacterial enzyme.

5. The method of claim 4 wherein the chondroitinase is chondroitinase B.

6. The method of claim 1 wherein the individual has a skin disorder.

7. The method of claim 6 wherein the skin disorder is scleroderma or psoriasis.

8. The method of claim 1 wherein the individual has keloid scarring or is at risk of keloid scarring, or has pulmonary fibrosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent to a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.